Strong bonds make perfect relationships. Covalent interactions between antibiotics and polymeric matrix as a key factor of effective polyanhydride-based drug delivery systems

Infections, when pathogens cause diseases, are an inevitable part of life. Their fatality has decreased significantly since Alexander Fleming discovered penicillin in 1928. Although it is almost 100 years since antibiotics have saved our lives, the problem is not over. Infections are still one of the major causes of death, surgical complications, or serious decrease in the quality of life. According to the World Health Organization (WHO), respiratory tract infections are the fourth global cause of death. Also, many surgeries fail annually as a result of post-operative infection, and 2% of society suffers from chronic wounds that often may not be cured because of permanent infection. Moreover, our ability to combat infections weakens, as many pathogenic species develop resistance to multiple antibiotics. When the concentration of a bactericidal substance in the colonized environment is too low, some individuals develop resistance mechanisms such as neutralizing enzymes or clearance from the host cell. Then, few bacteria survive the therapy and proliferate, but this time, the whole population becomes resistant to the therapeutic. Moreover, the bacteria can transmit resistance genes to other strains due to so-called horizontal gene transfer. The evolution of multidrug-resistant pathogens is faster than our ability to develop new antibiotics. Therefore, WHO claims such microbes as one of the biggest threats to humanity in the modern world.

One of the possible cures for the emerging problem is to develop drug delivery systems (DDSs) that use various techniques to deliver the active pharmaceutical ingredients (APIs) to the side of action. Thanks to this approach, the therapeutic concentration in the right place is better maintained and there are fewer side effects, as the remaining drug is not spread around the body. Among many ideas, one of the most common is the use of micro- or nanocarriers loaded with APIs that can be administrated via several routes to the right spot where they gradually release the drug in a controlled manner. Unfortunately, many DDSs fail due to poor encapsulation efficiency (EE) – the capacity of drug carriers to entrap the bioactive substances – making them therapeutically and economically inefficient.

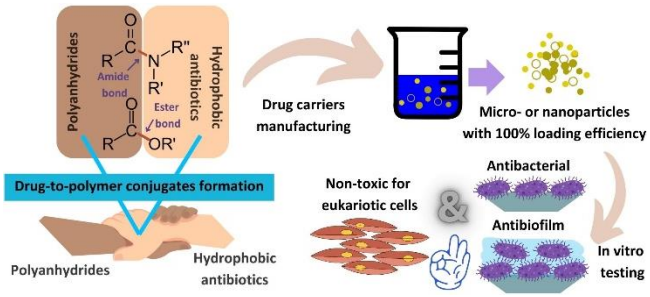

Fig. 1. Schematic representation of the project

In this project, we aim to obtain micro- and nanocarriers of antibiotics with 100% EE that may be used as DDSs for the lungs, bone tissue, and chronic wounds. The spectacular EE will be obtained thanks to the synthesis of drug-to-polymer conjugates due to the chemical reaction (either esterification or amide formation) between the polymeric matrix and drug molecules. Encapsulated antibiotics may not "run away" when they are chemically bonded to the matrix (Fig. 1). In turn, enzymes present in the biological environment can easily decompose the bonds, releasing the drug in its unaffected form directly to the place of infection.

During our 3 year project, we will perform screening research of commonly used antibiotics to determine which are capable of reacting with polyanhydrides, a special group of degradable polymers usually considered as a matrix for various micro- or nanocarriers of drugs. The best-performing drug-polymer combinations will designed as drug carriers meeting the requirements for drug delivery in terms of size, surface properties, degradation rate, and drug release. We will check them in various possible applications, such as an ink component for 3D printing to obtain antibacterial biomaterials. We will also test the drug carriers with cell cultures to make sure that they do not exhibit toxicity. In the last stage of the project, the formulations will be in contact with bacteria to ensure their potential to kill pathogens and treat infections. Ultimately, we aim to evaluate the best combination of drug-polymer in terms of successful conjugate formation that will exhibit sufficient physicochemical and biological properties to combat specific infections and solve the problems with limited therapeutic efficiency and growing antibiotic resistance.